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13. ABSTRACT (Maximum 200 words) The recent ability to test for an inherited susceptibility to breast cancer raises questions about the use of radiation therapy in patients with inherited mutations in BRCA1, BRCA2, or other breast cancer susceptibility genes. The presence of a mutation in a tumor suppressor gene, such as BRCA1, may have implications for patient management if patients with these mutations can be identified. Specifically, treatments such as breast conserving surgery and radiation therapy may be inappropriate if these patients are likely to be more susceptible to radiation-induced carcinogenesis or if they are more likely to recur locally in the breast because of multicentric disease. We have to date identified 90 eligible patients diagnosed with breast cancer at age 38 or younger and treated at the Joint Center for Radiation Therapy (JCRT) between 1987-95 of the 263 whom we expect to eventually contact. We have begun contacting these patients for a questionnaire/blood draw session. Lymphocytes from these patients will be collected and immortalized. At the end of the two year collection period, testing for the presence of a germ-line BRCA1 mutation will be performed. Treatment outcome will then be compared between the groups of patients with and without mutations in BRCA1.				
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FOREWORD

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INTRODUCTION:

This study will investigate the treatment outcomes after conservative surgery and radiation therapy among a cohort of young breast cancer patients who have BRCA1 mutations and a similarly-aged group who do not have mutations in BRCA1. The blood of young patients diagnosed with early-stage invasive breast cancer will be drawn and tested for the presence of mutations in the tumor suppressor gene BRCA1. At the end of three years, treatment outcomes will be compared between the patients in this group who have a mutation in the BRCA1 gene and those patients who do not. Blood will also be stored in order to test for mutations in other breast cancer susceptibility genes as such genes are identified and testing becomes available.

Breast conserving treatment has become a standard option for the majority of patients with early-stage breast cancer based on the results of randomized clinical trials demonstrating equivalent results to mastectomy (1). However, the recent ability to test for inherited susceptibility to breast cancer has raised questions about the use of radiation therapy in patients with inherited mutations in BRCA1 or BRCA2. The presence of a germ line mutation in a tumor suppressor gene, such as BRCA1, may have implications for patient management if patients with these mutations can be identified. Specifically, treatments such as breast conserving surgery and radiation therapy may be inappropriate if these patients are likely to be more susceptible to radiation-induced carcinogenesis or if they are more likely to recur locally in the breast because of multicentric disease (2,3).

The dose of radiation to the opposite breast from standard breast irradiation is typically several Gy, and this dose has been shown to induce breast cancer in young women. Indeed, recent studies have suggested that young age at the time of radiation may be the most important factor in determining the risk of radiation induced breast cancer. In a recent analysis of Connecticut Tumor Registry data by Boice (4), for example, the association between radiotherapy and the risk of contralateral breast cancer was highest among women who had breast cancer diagnosed before the age of 35. Young women with breast cancer are also most likely to have an inherited susceptibility to the disease.

Further data to suggest the potential tumorigenicity of radiation therapy in patients with BRCA1 mutations comes from evidence suggesting that patients with inherited mutations of other tumor suppressor genes may be susceptible to radiation induced tumors. Among 151 patients with Li-Fraumeni syndrome, for example, seven of eighteen subsequent tumors arose within the radiotherapy field. (5) Inherited mutations of other genes associated with an inherited tumor susceptibility, such as RB1 for retinoblastoma, also seem to increase the rate of radiotherapy induced second cancers. Eng et al. (6) have shown, for example, a nearly threefold higher mortality from second tumors among children with bilateral retinoblastoma who received radiotherapy as compared with bilateral nonirradiated patients.

Data which supports the concern for an increased risk of local recurrence in patients with an inherited susceptibility to breast cancer comes from Hiramatsu (7) who reported on a series of 76 patients treated with conservative surgery and radiation therapy for ductal carcinoma in situ. In this series, 17 patients had a positive family history of breast cancer in a first- or second-degree relative. In patients with a positive family history, the 10-year actuarial rate of local recurrence was 37% as compared with 9% in

patients with a negative family history ($p=0.008$). Furthermore, of the 17 patients with a positive family history, four developed either an ipsilateral or contralateral invasive breast cancer, whereas 1 of the 58 patients without a family history developed a subsequent invasive breast cancer ($p=0.008$). This finding has also been noted in a similar series of patients treated with conservative surgery and radiation therapy for DCIS in which 40% of patients with an ipsilateral breast recurrence had a positive family history in a first-degree relative, compared with 11.4% for those who did not have a local recurrence (8).

Despite the significant concerns raised by these issues, there have as yet been no studies performed to explicitly examine the relationship between treatment outcome after breast-conserving therapy and inherited susceptibility to breast cancer. The identification of the BRCA1 gene sequence and recent techniques to test for mutations of BRCA1 in individual patients now permits this study to be done. However, relating genetic mutations to outcome will only be possible among a large cohort of young patients with early-stage breast cancer treated in similar fashion, of which few exist. The resources of the Joint Center for Radiation Therapy, through the Dana Farber Cancer Institute, are uniquely suited to enable this study to be performed.

A second objective will be to determine patient preferences regarding the optimal time to consider genetic testing for breast cancer susceptibility genes in this patient population. Since the results of testing may influence local treatment decisions, patient preferences for the timing of testing assume added importance. Although analysis of genetic markers of breast cancer susceptibility is now technically feasible, it is not yet widely available and is early in its incorporation into clinical practice. Before testing was available, women unaffected but concerned about breast cancer risk expressed significant interest in undergoing testing in the future (~80%)(9). Recently, uptake of BRCA1 testing in members of extended families with identified mutations, studied in a structured testing program, was 43% overall but 74% among cancer patients (10).

Much data exist demonstrating that first-degree relatives of recently diagnosed breast cancer patients recognize the newly-increased breast cancer risk conferred by the relative's diagnosis. If clinical outcomes are shown to be different in women who have germline alterations in cancer-predisposing genes like BRCA1 compared to women who do not, then discussions regarding genetic testing will appropriately be conducted at cancer diagnosis, or when primary treatment decisions are made. In the absence of such proven medical value of testing, physicians may still wish to discuss testing issues with patients at various points along their paths from diagnosis and treatment, to relapse and advanced disease. Little is known about the patient perceptions of the optimal time to consider testing, or about the extent to which such decisions are influenced by time from diagnosis, family history, age, or other issues. Patient preferences, however, should influence medical practice in this arena which is currently being defined.

BODY:

Methods: We have to date identified 90 eligible patients diagnosed with breast cancer at age 38 or younger and treated at the Joint Center for Radiation Therapy at Harvard Medical School between 1987-95 of the 263 whom we expect to eventually contact. We have begun mailing letters to these patients to request participation in this study and have attained an initial response rate of 86%.

The blood collection protocol has been altered from the initial proposal such that we now intend to immortalize lymphocytes from each patient's blood sample to allow for adequate supplies of DNA to permit testing for other gene mutations (such as BRCA2)¹. Once transformed, aliquots of these cells will be frozen for later BRCA1 testing as specified in the original protocol. To date, 7 patients have been contacted and 4 have appointments scheduled to answer the questionnaire and to have their blood drawn. Two patients have completed the protocol and have had their lymphocytes immortalized. This is in line with the statement-of-work submitted with the initial protocol.

Results: See above. No data has yet been generated from this study. There are currently no negative nor positive findings related to this project.

Recommendations related to statement-of-work: We are currently on target with regards to the statement-of-work submitted with the initial grant proposal. We will accelerate identification of the remaining eligible patients and are in the process of ramping up enrollment and collection of blood samples. Genetic testing is scheduled to be performed during the third year of this protocol by which time all of the specimens should be collected and immortalized.

CONCLUSIONS:

Currently we are on target to collect blood specimens for DNA analysis on all eligible patients. There are currently no positive nor negative findings from this project.

REFERENCES:

1. M. A. Anderson and J. F. Gusella, *In Vitro* **20**, 856 (1984).